recite " the outer surface of each of said particles comprises hydrolyzed graphite." Support for these amendments is found at page 3, line 29 to page 4, line 2. No new matter has been added.

Claim 41 has been amended to more particularly point out and distinctly claim the present invention. Specifically, the claim has been amended to recite "at least an outer layer of said layers being chemically modified to provide improved chemical association of the modified layers with aqueous solution relative to non-modified layers, thereby forming a stable aqueous colloid." Support for this amendment is found at page 3, line 29 to page 4, line 2. No new matter has been added.

Claims 61 - 63 have been amended to more particularly point out and distinctly claim the present invention. Specifically, these claims have been amended to recite "wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles." Support for this amendment is found in the description of surfactant coated reagent particles at page 6, line 29 to page 7, line 2. Additional support for this limitation may also be found in the description of ThromboTrace, on page 10, lines 8 and 9. No new matter has been added.

New claims 64 -67 have been added. Support for these claims is found on page 2, lines 10 to 14. In addition, support is found in the description of an exemplary nanocolloid suspension, FullerTag, on page 10, lines 4 to 8. No new matter has been added.

New claims 68 - 70 have been added. Support for these claims is found in the description of an exemplary embodiment, ThromboTrace, on page 10, lines 8 - 9. No new matter has been added.

New claims 71 - 79 have been added. Claims 71, 73 and 78 recite that "the outer surface of each of said particles is hydrolyzed graphite." Support for these claims is found is found on page 4, line 2. Claims 74 and 76 recite that "the outer surface of each of said particles is hydrophilic." Support for these claims is found on page 3, line 29. Claims 72, 77, 78 and 79 recite "said colloid is lyophilic." As widely understood by persons of ordinary skill in the art of colloid science, the term lyophilic refers to a class of colloids characterized by the existence of stabilizing, associative chemical interactions between the dispersed and continuous phases. In the context of the dispersion of carbonaceous particles into a continuous aqueous phase, hydrolyzed and/or hydrophilic particle outer surfaces inherently provide for the formation of a lyophilic colloid. Therefore, new claims 72, 77, 78 and 79 are fully supported by the description of preferred embodiments beginning on page 3, line 29 and ending on page 4, line 6. No new matter has been added.

The amendments and remarks as presented here are believed to place the case in condition for allowance. Accordingly, entry of these amendments, reconsideration of the rejections and passage to allowance is respectfully requested. With this response claims 31 - 79 are pending.

The Rejections under 35 U.S.C. § 112, second paragraph

Claims 31, 32, 41, 42, 50, and 61-63 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as the invention. Applicants traverse certain aspects of this rejection and have amended the claims in response to other aspects of this rejection.

The term "some" in claims 31, 32, 41 and 50 is allegedly vague and indefinite. Applicants maintain that, as used in the rejected claims, the term "some" clearly refers to a portion of the discrete particles f the present invention. To expedite prosecution and

without acquiescing to this rejection, however, claims 31, 32, 41 and 50 have been amended to exclude reference to the allegedly vague term.

The term "fibrin-containing source" in claim 32 is allegedly vague and indefinite. To expedite prosecution and without acquiescing to this rejection, the claim has been amended and now recites "a sample containing fibrin." Although Applicants maintain the previous recitation was clear, approval of the amended language is respectfully requested.

The term "stable" in claim 42 is alleged to be "relative, as there is no means to compare what stable or unstable means when recited in the context of the claims and specification." Applicants respectfully disagree with the examiner's interpretation of this term. In reference to a colloidal suspension, "stable" is a well known term of art signifying a physical state characterized by colloidal particles having an interface occupied by ions, molecules or both present in the medium they are dispersed in. A "stable" colloidal suspension refers to colloidal particles in which the interfacial layer of ions, molecules or both present in the medium substantially prevents aggregation of individual particles and subsequent precipitation. In the interest of expediting prosecution and without acquiescing to this rejection, claim 42 has been amended and now recites "at least an outer layer of said layers being chemically modified to provide improved chemical association of the modified layers with aqueous solution relative to non-modified layers, thereby forming a stable aqueous colloid."

The term "increases" in claims 61 – 63 is allegedly "a relative term which renders the claims indefinite." To expedite prosecution and without acquiescing to this rejection, claims 61 – 63 have been amended and now recite "wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles." Applicants submit that reference to "increases" in amended claims 61 – 63 is not indefinite because the amended claims clearly refer to increases in the binding efficiency of particles having a surfactant coating with

fibrin relative to the binding efficiency of particles not having a surfactant coating with fibrin.

The Rejections under 35 U.S.C. § 103

Claims 31 – 63 have been rejected under 35 U.S.C. 103 as allegedly unpatentable over Burch *et al.* (Nuc. Med. Communications) in view of Chignier *et al.* (Biomat.) in further view of Watson et al. (WO 93/15768) and Senden *et al.* (J. Nuc. Med.). Applicants respectfully traverse this rejection.

The methods and reagents in the amended claims relate to stable diagnostic colloids comprising carbonaceous particles dispersed in aqueous media. Specifically, the physical and chemical properties of the outer surfaces of the particles of the present invention are selected to provide stable chemical association of the outer layer of each particle with an aqueous medium and effective, highly selective binding to fibrin. The combination of these physical and chemical properties provides for the diagnostic and drug-targeting function of the present invention. Amended claims 31 – 63 are not rendered unpatentable by the cited references because the combination of references fails to teach or suggest diagnostic particles capable of forming stable aqueous colloids. Rather, the cumulative disclosure raised by the Examiner is limited to colloidal suspensions comprising non-aqueous particles dispersed in gaseous media.

Contrary to the Examiner's characterization, the particles described in Burch *et al.* are not "technetium-99m compounds in aqueous aerosols." While the diagnostic particles in Burch et al. are derived from a solution of sodium pertechnetate in normal saline, the reference teaches "evaporating [the solution] to dryness" in a graphite crucible at a "temperature of 2500° C in an atmosphere of pure argon." (see Burch *et al.*, pg. 866, lines 18 – 24). This interpretation of the composition of the particles disclosed in Burch *et al.* is confirmed by the Inventor's declaration shown in Exhibit A. Burch *et al.* does disclose diagnostic particles comprising " 'soot', i.e. structured aggregates of carbon." However, the diagnostic reagents of Burch *et al.* differ substantially from the colloids

employed in the present invention. First, the carbonaceous particles in Burch *et al.* are suspended in an argon gas medium and, thus, are not capable of efficient delivery to aqueous samples containing soluble or insoluble fibrin. Second, the "soot" particles described in Burch *et al.* are not capable of stable association with aqueous media because of the highly aromatic (and hydrophobic) character of their outer surfaces. Although "soot" may comprise a variety of forms, including graphite, glassy carbon, and fullerenic carbon, all of these carbonaceous materials are thermodynamically unstable in an aqueous environment and, therefore, rapidly aggregate into larger particles and are lost upon dispersion. Accordingly, Burch *et al.* does not disclose, enable or suggest stable colloidal suspensions comprising carbonaceous particles dispersed in aqueous media.

Although Burch *et al.* mentions use of "aqueous aerosols of technetium-99m compounds by Taplin and . . . colleagues," the cited references **do not** refer to carbonaceous particles or particles dispersed in aqueous media. Rather, the methods of the references cited by Burch *et al.* are limited to diagnostics comprising droplets of aqueous solution containing solvated technetium compounds. In contrast to the diagnostic colloids of the present inventions, these references describe colloids dispersed in gaseous media. Further, the diagnostic markers disclosed in these references comprise technetium solutes rather than technetium containing particles. Accordingly, the references cited by Burch *et al.* do not disclose, enable or suggest colloidal suspensions of particles dispersed in aqueous media or diagnostic preparations containing radiolabeled carbonaceous particles.

The distinction between the physical and chemical properties of the diagnostic colloids of the amended claims and those described in the cited references is substantial. First, the carbonaceous particles of the present invention are in their active form (i.e. bind to fibrin) in the aqueous phase. Unlike the particles in Burch *et al.*, the particles of the present invention are capable of binding fibrin in a wide range of *in vivo* and *in vitro* aqueous settings, particularly physiological settings involving the circulation system. Second, the carbonaceous particles of the present invention are present as a stable colloid

due to the associative interactions of their outer surfaces with aqueous media. Therefore, carbonaceous particles of the present invention are capable of remaining dispersed in the aqueous phase for long times corresponding to long diagnostic observation times. In contrast, the diagnostic particles disclosed in Burch *et al.* have extremely hydrophobic outer surfaces and, hence, are rapidly lost by coagulation and coalescence upon dispersion into aqueous media. Third, modification of the particles disclosed in Burch et al. to provide for stable association with an aqueous medium would have been well outside the grasp of the ordinary skilled artisan at the time of the invention because the aromatic carbon surface layers of such particles are extremely stable and highly hydrophobic.

To clarify the precise physical and chemical properties of the diagnostic colloids employed in the present invention, the claims have been amended to provide that "the outer surface of said particles allows for a stable chemical association with an aqueous medium" and "upon administration of said reagent said particles are dispersed in the aqueous medium and form a stable colloid." The combination of references cited by the Examiner, does not enable, disclose or suggest particles capable of forming a stable colloid in aqueous media. It is therefore submitted that no *prima facie* case of nonobviousness has been made out because the references, when combined, do not teach or suggest all the limitations appearing in the amended claims. MPEP § 706.02(j)

In addition, there is no suggestion or motivation in the combination of references to combine the diagnostic particles disclosed in Burch *et al.* with teachings relating to use of carbonaceous materials in aqueous environments. The Examiner characterizes Chignier *et al.* as teaching the "haemocompatibility and biological course of carbonaceous composites for cardiovascular devices." Without any motivation or suggestion to combine these teachings, however, there is insufficient teaching to enable a person of ordinary skill in the art at the time of the invention to integrate teachings related to cardiovascular implants to the diverse setting of colloidal diagnostics. Applicants submit that no prima facie case of nonobviousness has been made out because there is no suggestion or

motivation to combine the teachings of the cited references. In re Vaeck, 947 F. 2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

Moreover, the Burch *et al.* reference actually teaches away from the use of carbonaceous particles that form stable colloids in aqueous media. As described in the Declaration in Exhibit A, the express aim in Burch *et al.* is to provide gas-like diagnostic particles for imaging lung tissue, which do not suffer from the "many limitations" of aqueous radioactive tracers, (see, Burch *et al.*, pg, 866, lines 4 – 10 & pg. 867, lines 27 - 32). Such limitations include the loss of aqueous tracers across the blood-air barrier in the lung. Indeed, Burch *et al.* reports the benefits of non-aqueous radioactive tracers exhibiting no "clearance . . . from the lungs" and having long diagnostic half-lives. Since the Burch *et al.* reference teaches away from a limitation in the amended claims, it cannot serve as the basis of an obviousness rejection. Gillette Co. v. S.C. Johnson & Sons, Inc., 919 F.2d 720, 724, 16 U.S.P.Q2d 1923, 1927 (Fed. Cir. 1990). Applicants have amended the rejected claims to better claim the invention and request reconsideration and withdrawal of the rejections in light of the foregoing arguments.

CONCLUSION

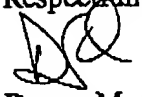
In view of the foregoing arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This Amendment is accompanied by a Request for Continued Examination. Authorization is given to charge Deposit Account 07-1969 the amount of $750.00, as required by 37 C.F.R. 1.17, and $162.00 for the presentation of nine additional dependent claims, as required by 37 C.F.R. 1.16(c). If the amounts described are incorrect, please

deduct the appropriate fees for this submission and any extension of time required from Deposit Account No. 07-1969.

Respectfully submitted,



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bmk: January 27, 2003

Marked up version of amended claim(s) in attached Amendment.

Docket No.: 5-00
USSN 09/463,082
Filed: July 10, 2000

31. (Once amended) A method for the *in vivo* detection of fibrin, said method comprising the steps of:

administering to said patient an effective amount of a detectable reagent comprising discrete particles dispersed in a pharmaceutically or veterinarily acceptable carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise a detectable marker encased in at least two layers of carbon, wherein the outer surface of said particles allows for a stable chemical association with an aqueous medium and wherein upon administration of said reagent said particles are dispersed in the aqueous medium and form a stable colloid;

binding [at least some of] said particles to said fibrin; and

detecting the presence of said detectable marker in said patient.

32. (Once amended) A method for the detection of fibrin in a [fibrin-containing source] a sample containing fibrin, said method comprising the steps of:

supplying to said [fibrin-containing source] sample containing fibrin a detectable reagent comprising discrete particles dispersed in a carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise a detectable marker encased in at least two layers of carbon, wherein the outer surface of said particles allows for a stable chemical association with an aqueous medium and wherein upon administration of said reagent said particles are dispersed in the aqueous medium and form a stable colloid;

binding [at least some of] said particles to said fibrin; and

detecting the presence of said detectable marker in said [fibrin-containing source] sample containing fibrin.

33. (Once amended) The method according to claim 31, wherein the outer surface of each of said particles is hydrophyllic [and comprises said detectable marker encased in from 2 to 10 layers of graphitic carbon].

41. (Once amended) A detectable reagent for use in *in vivo* or *in vitro* detection of fibrin, said detectable reagent comprising discrete particles dispersed in a carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise a detectable marker encased in at least two layers of carbon, wherein [at least some of] said particles preferentially bind to fibrin over other blood plasma proteins and wherein the outer surface of said particles allows for a stable chemical association with an aqueous medium and wherein upon administration of said reagent said particles are dispersed in the aqueous medium and form a stable colloid.

42. (Once amended) The detectable reagent according to claim 41, wherein each of said particles comprises a detectable marker encased in from 2 to 10 layers of graphitic carbon, at least an outer layer of said layers being chemically modified to [enable a stable] provide improved chemical association of the modified layers with aqueous solution relative to non-modified layers, thereby forming a stable aqueous colloid.

43. (Once amended) The detectable reagent according to claim 41, wherein the outer [layer] surface of each of said particles comprises hydrolyzed graphite.

50. (Once Amended) The method of targeting a drug to a localized fibrin site *in vivo*, the method comprising the steps of:

administering to a patient an effective amount of a reagent comprising discrete particles dispersed in a veterinarily or pharmaceutically acceptable carrier, diluent, excipient, adjuvant or any combination thereof, wherein [at least some of] said particles comprise at least two layers of carbon and [at least some particles] have coupled thereto a drug to be targeted to the localized fibrin site, wherein the outer surface of said particles allows for a stable chemical association with an aqueous medium and wherein upon administration of said reagent said particles are dispersed in the aqueous medium and form a stable colloid; and

binding [at least some] of said particles to said localized fibrin site;

whereby said drug is targeted to said localized fibrin site.

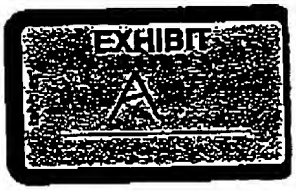
53. (Once amended) The method according to claim [42] 50, wherein the outer surface of each of said particles [of hydrophilic and compromise said detectable marker encased in from 2 to 10 layers of graphitic carbon of said particles] is hydrophilic.

61. (Once amended) The method according to claim 31, wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles.

62. (Once amended) The method according to claim 32, wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles.

63. (Once amended) The detectable reagent of claim 41, wherein a surface of said particles is coated with a surfactant coating that increases the binding efficiency of said coated particles with fibrin relative to uncoated particles.

IN THE MATTER f United States Patent Application No. 09/463082 in the name of The Australian National University



STATUTORY DECLARATION

I, Timothy John Senden, of 27 Bandjalong Crescent, Aranda, ACT 2614, Australia, do solemnly and sincerely declare as follows:

1. I am an inventor of the invention which is the subject of United States Application No. 09/463,082 (hereafter "the application") and I am well acquainted with the specification filed in respect of the application, including the invention defined in the claims of the application. Furthermore, I am acquainted with the Official Actions which have issued in respect of the application, including the Official Action dated 27 June 2002. I am also well acquainted with the documents raised as citations during examination of the application, including Burch et al (Nuc. Med. Communications), Chignier et al (Biomat.), Watson et al (WO 93/15768) and Senden et al (Journal of Nuclear Medicine).

2. It is my understanding that the Examiner has maintained objection to the claims of the application on the basis of the four documents referred to in the preceding paragraph on the basis that Burch et al discloses "Technegas" to be a carbon-based aqueous aerosol which includes Technetium-99m and the use of such aqueous aerosols for imaging of lung tissue via inhalation; that Chignier et al illustrates that carbon binds to fibrin; that Senden illustrates that Technegas contains discrete radio-labelled fullerenes; and finally that Watson illustrates carbon particles as diagnostic and therapeutic agents. I understand that the Examiner believes that the combination of these documents would lead one of ordinary skill in the art to the invention which is defined in the applicati n. I have been asked as an inventor in respect of th invention which is the subject of the application to provide my comments on the Examiner's argument given my understanding of the invention, the application (including the claims as defined in the application) and particularly given my understanding of the citations

raised.

3. Firstly, dealing with Burch et al, I note that this document does not in fact relate to wet or aqueous aerosols. Rather, Burch et al teaches the opposite of such aerosols. In this regard, the Examiner has pointed to a brief mention of an "aqueous aerosol" on page 865, third paragraph, but has apparently failed to realise that this disclosure is in fact in relation to the prior art and is provided in Burch et al only as a means of comparison with the invention of Burch et al.

4. In Burch et al, Burch contrasts the poor efficacy of wet aerosols with his novel product in which a technetium compound is reduced at elevated temperatures. Burch et al plainly describes an aerosol produced in the *absence* of all water (see Methods section)

> "In summary, the procedure involves the evaporation to dryness of 140 MBq of sodium pertechnetate in normal saline (standard generator eluent) in a graphite crucible. The crucible is heated to 2500°C in an atmosphere of pure oxygen for 15 s. ".

5. Burch et al states that this product, upon inhalation diffuses down to "and adheres to the alveolar walls".The depth of penetration and the lack of transport across the blood-air barrier is not typical of , an ordinary wet aerosol. If this product was "wet" it would certainly cross the blood-air barrier in the lung. Further, the distinction between a true gas and Technegas is made by Burch et al. The penetration index for Technegas exceeds unity, which indicates the lack of mobility of the product (adherence) within the lung compared with the equilibrium diffusion of true gases.

6. Finally, it is my understanding from Burch et al that the aim was to illustrate a novel device for the production of "gas-like" species from suitable radio-isotopes of medical value corresponding with a clear teaching away from the use of aqueous aerosols, as clearly indicated by the comparative reference to such aerosols in Burch et al. As such, Burch et al falls well short of the teaching described by the Examiner in the

recent office action of 27 June 2002.

7. Chignier et al demonstrates the biocompatability of vitreous or glassy carbon. The emphasis of the work of Chignier et al is on the integration of this form of carbon into prosthesis. The material is described as "rough and porous" and shows short term depositions of fibrin and other blood proteins, particularly collagen. However, the work of Chignier et al focuses on the general conclusion that "at two months both arterial and intracardiac implants were free of any thrombotic deposit, the whole implant was covered macroscopically by a thin membrane." This is to state that glassy carbon does not support long term fibrin deposition. The work "emphasizes the importance of the physical properties of the material surface" which contrasts with the invention and chemical claims of the application.

8. Finally, I note that glassy carbon is not graphitic, nor fullerenic. It is half way between diamond and amorphous carbon. As such, Chignier et al does not illustrate that fibrin adheres to carbon particles in accordance with the present invention as suggested by the Examiner. I note that a chemist would not confuse the forms of carbon defined in the claims of the application with those described in Chignier et al.

9. Turning to Senden et al, the Examiner has suggested that Senden has been relied upon for teaching that Technegas contains discrete radio-labelled fullerenes. In fact, Senden et al deals with the structural and chemical elucidation of Technegas and does not address the structure of the particle described in the application directly, but rather a modified form of it. Importantly, Senden et al states that Technegas is not a fullerene.

10. Senden et al state;

> "No evidence for the presence of TcC [technetium carbide] was found in the aerosol output. Force microscopy of the surface of the technetium platelets revealed a covering with a layer of graphite. Two arguments could be used against the presence of a technetium-fullerene species. First the great bulk of technetium aerosol can be accounted for as hexagonal platelets. Second, the conditions are far from optimal for the efficient production of fullerenes."

11. In conclusion, Senden et al states emphatically that "Technegas particles are hexagonal platelets of metallic technetium, each closely encapsulated with a thin layer of graphitic carbon". The use of "graphitic" separates the structure of the carbon from that of fullerenes without ambiguity.

12. Watson et al does not specify the method of production detailed and predated by Burch et al. The work of Watson et al does not stand up against the recent and numerous applications claimed for fullerene-based drugs and so I do not believe that it can be effectively used against a non-fullerene as defined in the application. Further, the combination of Watson et al with the work of Senden et al cannot lead to the material claimed in the application. Specifically, Watson et al does not describe in any form fibrin labelling and Senden et al does not demonstrate the preparation of material for injection.

13. Still further, the combination of Burch and Chignier is equally unproductive. The Burch et al product cannot be dispersed in aqueous media, nor does it have the chemical form or physical structure of the Chignier et al carbon. The Chignier et al material is expressly for prosthetic devices and requires bio-compatibility, not the singular reaction to the blood protein, fibrin. I note that no other affinity with any other blood protein is claimed in the application.

14. Further to the above, I believe that even the full combination of the four documents cited by the Examiner does not arrive at the invention of the application. None of the citations employ the correct method of particle capture and conversion into an aqueous dispersion for administration.

AND I MAKE this solemn declaration by virtue of the Statutory Declarations Act 1959 as amended and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true and correct in every particular.

DECLARED at Canberra in the State of ACT
this 21st day of October, 2002

Timothy J Sande

Before me: Cindy Bradley